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(54) Sucralfate preparations for application on esophagus mucosa.

(57) A sucralfate preparation in the form of a suspension which is suitable for curing esophagitis or esophageal ulcer and a method of preparation thereof are disclosed. The sucralfate preparation comprises sucralfate suspended in an aqueous solution or aqueous suspension of water-soluble or water-insoluble polymeric substance as a suspending agent or thickening agent and has a viscosity in the range from 1,000 to 5,000 cP. This sucralfate preparation adheres selectively to ulcerated or inflammatory sites of the esophageal mucosa and is very effective as a cure for esophagitis or esophageal ulcer.

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SUCRALFATE PREPARATIONS FOR APPLICATION ON ESOPHAGUS MUCOSA

This invention relates to sucralfate preparations for application on esophagus mucosa.

An aluminum salt of sucrose sulfate ester (conventionally known as sucralfate) is an excellent ulcer curative agent with minimal side effects, and is extensively used in anti-ulcer therapy.

Sucralfate is characterized by anti-pepsin and anti-acid effects in that it binds to the pepsin and acids in gastric juice, which are two agents that attack the ulcer-affected area of digestive tracts, and thereby inhibits their activities directly. Sucralfate is also characterized by its ability to protect the mucosa in that it forms a sucralfate coat on the mucosa of the digestive tract and protects it from the attacking agents. These effects combine to provide sucralfate with high anti-ulcer activities. It has also been found that sucralfate is effective in revascularization and in accelerating the growth of regenerated mucosa, and hence is considered to have a great potential for use in promoting the healing of ulcers.

Sucralfate has an ability to selectively bind to the ulcer-affected mucosa of the digestive tract rather than the normal mucosa of the digestive tract and form a protective coat against the invasion of attacking agents. This ability is the most characteristic feature of sucralfate, not found in other anti-ulcer treatments. The Esophagus differs in function from other digestive organs, in that it is not concerned with the digestion of foods, absorption of the nutrients, etc.; but instead plays an important role in transporting foods from the oral cavity to the intraperitoneal digestive tract. In a normal person the digestive liquid which has been regurgitated from the stomach to the esophagus may be returned immediately by the action of vermiculation of the esophagus. However, if regurgitation occurs frequently or if the regurgitated gastric juice or bile is retained in the esophagus, then regurgitational esophagitis will develop. Another type of regurgitational esophagitis, not associated with actual regurgitation symptoms, is also known. This type of esophagitis is considered to be caused by various factors which have an affect upon each other. It is also known that this type of regurgitational esophagitis repeatedly results in recrudescence and relapse of diseases, and that a long period of time is required for therapy and observation in the subsequent curing process. Further, this disease is associated with deformation and stricture of the esophagus. For these reasons, this type of esophagitis is recognized to be very difficult to cure and has been mainly treated by surgical means.

In the primary stage of the disease, nonserious regurgitational esophagitis may usually be cured by alimentary therapy and/or by controlling the patient's daily routine. However, if the disease is more serious or is associated with other diseases, simple alimental therapy is not sufficient to cure the disease effectively and a more positive treatment using drugs is required.

In case it is intended that a pharmaceutical preparation be orally administered and adhered on inflammatory sites in wet tissue such as those formed in esophageal mucosa, the administration of a preparation in the form of tablet, troche or sublingual tablet is unable to readily provide such desired effects as binding or adhering of the pharmaceutical preparation to the inflammatory sites because a patient often swallows or crunches the solid preparation.

These problems can not be solved by simply increasing the dose level of the drug. On the other hand, the administration of an effective component in the form of powder will not provide the desired effects for several reasons, typically because the administration of a powdery preparation is associated with pain.

On the other hand, a preparation in the form of a suspension has advantages in that the dose level can be easily controlled, and in that it is a very easy form for oral dosage. Under these circumstances, the inventors of this application extensively studied the dosage form of sucralfate in order to fully develop its above-mentioned advantages by the use of a suspension dosage form. In general, it has been believed that from the practical and organoleptic viewpoints, a suspension having a viscosity of higher than 500 centipoise (cP) is difficult to use clinically, and that it is preferable to use a suspension with a viscosity of lower than 50 cP, especially from the organoleptic viewpoint. With this knowledge, the inventors formulated various types of sucralfate preparations with less than 500 cP at 20°C. These preparations include suspensions without any suspension stabilizer or thickener; suspensions containing a water-insoluble or water soluble polymeric substance as a suspension stabilizer or thickener; suspensions containing a thickener such as glycerine, sucrose or sorbitol; suspensions formulated by using sucralfate having particles of predetermined and relatively uniform sizes; suspensions containing various additives such as sugars, salts, acids, bases, or the like; suspensions having various concentrations of suspended particles; suspensions containing a surfactant for the purpose of changing their physical properties; suspensions prepared by varying the conditions of a homog nizing mixer; and suspensions using the above-mentioned conditions with a different suspension medium. These suspensions wer tested with respect to their selective binding to the ulcerated or inflammatory sites of esophageal mucosa. The suspension was forcefully administered through a probe into the esophagus of rats in which esophagitis had been artificially induced or which have

not been treated. The selective binding of sucralfate to ulcerated or inflammatory sites was determined by measuring the amount of sucrose sulfate and aluminum adhered to each of the ulcerated or inflammatory sites as well as sites which had not been ulcerated or were not inflammatory with respect to the resected pieces of mucosa having the same and predetermined size. Three hours after the adminstration of sucralfate, the rats were killed and the pieces of mucosa were prepared. The amount of each of aluminum and sucrose adhered on the samples was determined by the methods of Okamura et al., Bull. Chem. Soc. Japan, 31.783 (1958) and the method of Nagashima et al., "Arzneim-Forsch. 29. 1668 (1979)", respectively.

The results of the above-mentioned tests showed that no sucralfate was selectively adher d to any of the inflammatory sites with any of the formulated suspensions. It is believed that this phenomenon is due to secretions such as saliva washing off the suspension administered. Since it is impossible to completely eliminate this phenomenon, the inventors confirmed that none of the suspensions having the above-mentioned viscosity is suitable as a preparation for oral administration.

Under this situation, the inventors continued their studies and unexpectedly found that a suspension containing sucralfate and having a viscosity in the range of from 1,000 to 5,000 cP at 20°C most effectively adheres on the inflammatory sites and this invention was thereby completed. According to their further studies, the inventors found that the desired effects are not achieved if substances having low molecular weights such as sorbitol, sucrose, glycerine or the like are used for formulating a sucralfate-containing suspension in order to increase the viscosity of the suspension to a desired range.

In order to ensure that sucralfate effectively adheres to inflammatory sites, it is necessary that it is suspended in an aqueous solution or suspension of one or more water-soluble or water-insoluble, natural or synthetic or semi-synthetic polymeric substances and having a viscosity of from 1,000 to 5,000 cps.

The polymeric substances which are useful in this invention include water-soluble polymeric substances such as crystalline cellulose, such as one sold under the trade mark "Avicel RC-591NF", tragacanth gum, casein, arginic acid, starch, carboxymethylcellulose and calcium carboxymethylcellulose, water-soluble polymeric substances such as synthetic or semi-synthetic polymers, for example, methylcellulose (substitution degree: 1.6 - 2), ethylcellulose (substitution degree: 1 - 1.5), propylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxyethylpropylcellulose, hydroxypropylmethylcellulose, carboxymethylstarch, carboxymethylethylcellulose, carboxymethylhydroxyethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone and propyleneglycol arginic acid ester, and natural polymers, for example, gum arabic, dextrin, pruten, gelatin, xanthan gum, carggeenane, guar gum, locast bean gum, albumin and collagen. These polymers can be used alone or in admixture. Hydroxyethylcellulose and hydroxypropylmethylcellulose are especially preferable for providing the desired effects of this invention. The amount of polymer to be used in this invention may be determined based on the specific polymer used and the viscosity of the suspension. In addition, if desired, one or more appropriate additive, such as sweeteners, flavoring, preservatives, excipients and the like can be incorporated in the suspension of this invention. These additives may be used by selecting the species, amount, and incorporation manner in accordance with conventional practice for formulation of pharmaceutical preparations.

The invention is further illustrated by the following Examples which do not limit the invention.

Example 1

Crystalline cellulose (sold under the trade name of Avisel RC-591NF: 10 g) was preliminarily dispersed in distilled water in an agitating and homogenizing mixer. To the dispersion was slowly added DL-alanine (5 g) and then sucralfate (50 g) while stirring. After a preservative (0.4 g) had been added and the mixture stirred, water was added to bring the total volume to 500 ml to give a suspension which was used as a test sample.

The process as described above was repeated except that crystalline cellulose was not used, thus producing a suspension to serve as the control.

Example 2

Hydroxypropylmethylcellulose (7.5 g) was preliminarily dispersed in distilled water in an agitating and homogenizing mixer. To the dispersion was slowly added DL-alanine (5 g) and then sucralfate. After further adding a 70% D-sorbitol aqueous solution (25 g) and a preservative (0.4 g) to the mixture and stirring it, the mixture was treated as in Example 1 to give a suspension which was used as a test sample.

Separately, the method described above was repeated except that hydroxypropylmethylcellulose was not used, thus producing a suspension to serve as a control.

Example 3

Hydroxyethylcellulose (10 g) was dissolved in water. To the solution was slowly added DL-alanine (5 g) and, then, sucralfate (50 g) while stirring in a mixer. Then, sucrose (25 g) and a preservative (0.4 g) were added to the mixture which was treated as shown in Example 1 to give a suspension which was used as a sample of this invention.

Separately, the process described above was repeated except that hydroxyethylcellulose was not used, thus producing a suspension to serve as a control.

The experimental induction of regurgitational esophagitis has been tried. One of the known methods for inducing esophagitis comprises causing endogenous regurgitation by forming esophagocele but does not give constant results. Therefore, the inventors employed a method in which Wister-strain rats were used as test animals and an acid was injected in a lower part of the esophagus to induce esophagitis.

There is a criterion prepared by the Association of Esophageal Disease in Japan with respect to diagnosis for esophagitis on the basis of the histological view. The esophagitis induced in the test animals by the inventors was found to develop changes of tissue corresponding to those defined in the criterion. These were various cellular infiltrations in mucosa or submucosa, cellular infiltration of intrinsic muscle layer, or hemostatis or dilation of blood vessels in submucosa which often develop during the induction of esophagitis.

In accordance with these findings, the inventors conducted the following experiment.

Experiment

Wister-strain male rats weighing about 200 g were caused to fast for 48 hours, their abdomen opened, and pylorus ligated. In order to relax the tension of sphincter at a lower part of the esophagus, atropine (0.2 mg/kg) and then 2 ml of 1N hydrochloric acid were orally administered by use of a cannula to develop esophagitis with remarkable degeneration of mucosal epithelium, hemostatis and cellular infiltration. These tissue degenerations clearly developed about one hour after the treatment.

The sample or control which was prepared by each of the Examples was forcefully administered to the esophagitis-induced rats through a cannula. In this treatment, the test animals were divided into groups of six members each and the sample or control was administered in a dose of 0.5 ml per head in terms of suspension, or 50 mg per head in terms of sucralfate. Three hours after the administration, the rats were killed and the quantity of each of aluminum and sucrose sulfate ester adhered to the inflammatory sites of esophagitis was determined.

The results are shown in Table 1 below. As is clear from the test results, the values of aluminum and the ester with respect to the sample suspension were larger than those of the control.

Table 1

Examples	Test suspension	Viscosity (cP, 20°C)	Sucrose sulfate ester (µmol/cm²)	Aluminum (µmol/cm²)
1	sample	1080.0	1.458	2.458
	control	7.5	0.066	0.115
2	sample	1502.5	1.619	2.421
	control	8.3	0.019	0.043
3	sample	2030.0	1.589	2.356
	control	10.6	0.008	0.017

Claims

1. A sucralfate preparation in the form of a suspension having a viscosity of from 1,000 to 5,000 centipoise at 20°C.

2. A sucralfate preparation according to Claim 1 for use in the treatment of inflammations of esophageal mucosa.

3. A sucralfate preparation according to Claim 1 or 2 wherein said preparation comprises sucralfate suspended in an aqueous solution or suspension of one or more water-soluble or water-insoluble polymeric substances as a suspending agent or thickening agent.

4. A sucralfate preparation according to Claim 3 wherein said suspending agent or thickening agent is crystalline cellulose, hydroxyethylcellulose or hydroxypropylmethylcellulose.